REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 1-4, 7-14, 17-24 and 27-31 are pending in the present action.

Applicants have noted a typographical error in the June 16, 2007 Office Action. The Office Action Summary indicates that the Office Action is non-final, however, the Conclusion on page 6 of the Office Action indicates that the Office Action is final. Applicants have checked the PAIR entry for the June 16, 2007 Office Action and the entry indicates that the June 16, 2007 Office Action is non-final. In view of the Office Action Summary and PAIR entry, Applicants have assumed that the "Conclusion" is an inadvertent error and have treated the June 16, 2007 Office Action as a non-final Office Action.

DOUBLE PATENTING

On pages 2-3 of the Office Action, the Examiner provisionally rejected claims 1, 2, 4-6 and 8-10 on the grounds of non-statutory obviousness-type double patenting in view of claims 1, 20 and 33-40 of co-pending United States Patent Application No. 11/094,493.

The Examiner also provisionally rejected claims 1-31 on the grounds of non-statutory obviousness-type double patenting in view of claims 1-34 of co-pending United States Patent Application No. 10/777,542.

In an effort to expedite prosecution of the present application, submitted herewith is a terminal disclaimer for United States Patent No. 10/777,542. Applicants respectfully

traverse the double patenting rejection based upon Application No. 11/094,493.

Claims 1-38 of Application No. 11/094,493 recite a pharmaceutical dosage form exhibiting a controlled release of a first active ingredient and an immediate release of a thiazolidinedone derivative wherein the dosage form exhibits a "significantly higher bioavailability" of the thiazolidinedone derivative than conventional immediate release thiazolidinedone derivatives. It is respectfully submitted that the "significantly higher bioavailability" limitation of claims 1-38 renders these claims patentably distinct from the claims in the pending application.

The claims in the present application require a primary seal coat between the controlled release core and the immediate release thiazolidinedone derivative coat. As explained in the present application, Applicants have discovered the seal coat is important for proper adhesion to and release of the thiazolidinedone derivative from the controlled release core. Subsequent to discovering the need for the seal coat, Applicants discovered that the composition of the thiazolidinedone layer could significantly improve the bioavailability of the thiazolidinedone derivative. Not all compositions with a seal coat between the controlled release core and the thiazolidinedone layer will exhibit significantly higher bioavailability. This fact is demonstrated on page 32 of Application No. 11/094,493. The tables at the bottom of page 32 compare Reference Examples 2 and 3 which have a seal coat to Example 2 which also has a seal coat. The data shows that bioavailability of the thiazolidinedione derivative is dependent upon the composition of the thiazolidinedone coat. More specifically, if certain excipients are included in the thiazolidinedione coat, the bioavailability of the thiazolidinedione derivative can be

significantly increased.

Applicants respectfully submit that this discovery of a formulation that exhibits "significantly higher bioavailabilty", a limitation of claims 1-38 of Application No. 11/094,493, renders claims 1-38 patentably distinct from the claims in the present application.

Claims 39-41 of Application No. 11/094,493 recite an immediate release thiazolidinedone dosage form that exhibits a "significantly higher bioavailability" as discussed above for claims 1-38 of Application No. 11/094,493. Because claims 39-41 require an immediate release composition that exhibits a "significantly higher bioavailabilty" as discussed above and not a dosage form with a controlled release metformin core, primary seal coat and an immediate release thiazolidinedione derivative coat as recited in the pending claims, it is respectfully submitted that the pending claims are patentably distinct from claims 39-41 of Application No. 11/094,493.

Based upon the terminal disclaimer submitted herewith and the above remarks, it is respectfully requested that the provisional double patenting rejections be withdrawn.

35 U.S.C. § 112

On page 3 of the Office Action the Examiner rejected claims 1-31 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner rejected claims 1, 9-11, 21 and 29-31 under 35 U.S.C. § 112, second paragraph, because the term "thiazolidinedione derivative" is allegedly indefinite. Although Applicants believe the term "thiazolidinedione derivative" is definite for the

reasons of record, Applicants have amended independent claims, 1, 11 and 21 to recite that the "thiazolidinedione derivative" is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof. Applicants have also amended independent claim 31 to indicate that the thiazolidinedione derivative is pioglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof. No new matter is added by these amendments. Support can be found in dependent claims 6, 16 and 26 as originally filed. Based upon the amendment to the independent claims, dependent claims 6, 16 and 26 have been canceled without prejudice in the present amendment.

The Examiner also indicated that the seal coat recited in claims 3, 13 and 23 is confusing. In an effort to alleviate the confusion, Applicants have amended the independent claims and dependent claims 3, 13 and 23 to more clearly indicate that there are two separate and distinct seal coats. First, the independent claims have been amended to recite a "primary seal coat". The primary seal coat is therefore required by all the pending claims. The primary seal coat is a coating on top of or applied to the controlled release core and below the immediate release thiazolidinedione derivative coat. As discussed in detail in the February 14, 2007 submission, Applicants discovered that by applying an immediate release thiazolidinedione derivative coat to a primary seal coat (rather than directly to a controlled release core) the adhesion of the immediate release thiazolidinedione derivative coat to the dosage form was greatly improved without adversely affecting the release properties of the thiazolidinedione derivative.

The second seal coat is recited in dependent claims 3, 13, and 23. These claims

have been amended to indicate that the second seal coat is "a secondary seal coat". More specifically, dependent claims 3, 13, and 23 recite a dosage form wherein the controlled release core is an osmotic tablet. The osmotic tablet comprises a core that is optionally coated with the secondary seal coat which in turn is coated with a semipermeable membrane. The semipermeable membrane is then coated with the primary seal coat and the immediate release thiazolidinedione derivative coat.

No new matter is added by these amendments and support can be found in Examples 4, 5, and 6 on pages 18-23 of the present application.

Based upon the foregoing amendments, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

35 U.S.C. § 103(a)

On pages 4-8 of the Office Action, the Examiner rejected claims 1-31 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Vergez et al., United States Published Patent Application No. 2006/0204578 ("Vergez").

In response to this rejection, Applicants have amended the claims to specifically indicate that the claimed dosage form requires three separate and distinct elements. Specifically, each claim requires 1) a controlled release metformin core; 2) a primary seal coat applied to the metformin controlled release core; and 3) an immediate release thiazolidinedione derivative coat applied to the primary seal coat. In response to the Examiner's comments regarding the Vergez reference on pages 5 and 6 of the June 16, 2007 Office Action, Applicants have further amended independent claims 1, 11, 21 and 31 to indicate that the primary seal coat does not contain an active pharmaceutical

ingredient and that it rapidly disperses or dissolves in water. No new matter is added by this amendment. Support can be found on page 9, lines 28-30 of the present specification.

It is respectfully submitted that present amendments requiring the primary seal coat to rapidly disperse or dissolve in water further distinguishes the present claims from the Vergez reference.

On pages 5 and 6 of the June 16, 2007 Office Action, the Examiner relied upon ¶ 63 of the Vergez reference to maintain the obviousness rejection of the pending claims. According to the Examiner, ¶ 63 of the Vergez reference teaches an internal "microporous or permeable" layer below the optional immediate release layer. The "mircoporous or permeable" layer is quite different from the rapidly dissolving or dispersing primary seal coat of the present claims. It is readily apparent to an individual of ordinary skill that the "microporous or permeable membranes" of the Vergez reference are designed to regulate the release of drug or ingredients below the membrane and to remain intact for a substantial period of time after administration.

¶ 62 of the Vergez reference defines microporous as "a membrane that permits release of the active agent in the core by diffusion through micropores in a surrounding membrane." Diffusion of an active ingredient through a membrane is a well-known rate limiting process that is designed to control the rate at which a drug is released from a dosage form. Inherent in this definition is the need for the microporous membrane to remain around the dosage form after administration so the active ingredient can diffuse through the micropores. Similarly, ¶62 of the Vergez reference defines "permeable" as

permitting "passage of fluid and of ingredient(s)." Again, this definition suggests to an individual of ordinary skill that the internal layer remains intact for a substantial time period after administration thus allowing fluid and ingredients to pass through the membrane.

As recited in the amended claims, the primary seal coat rapidly disperses or dissolves after the dosage form is administered to a patient or placed in an aqueous environment. This is critical to the present invention because the thiazolidinedione derivative should be released immediately after administration; the metformin in the controlled release core should also begin release shortly after administration. In order to accomplish both of these tasks the primary seal coat should rapidly disperse or dissolve. If the primary seal coat does not rapidly disperse or dissolve after administration, the release rates of the thiazolidinedione derivative and metformin could be altered and adversely affect the bioavailabilty of the drugs.

Applicants do not dispute that the Vergez reference contains a broad general teaching of an immediate release coating, however, this broad general teaching combined with the specific teachings of the Vergez reference to prepare dosage forms with two (2) active ingredients in the controlled release core would not lead an individual of ordinary skill to the presently claimed invention without the improper use of hindsight.

The presently amended claims recite a once a day dosage form that comprises a controlled release core, a rapidly dissolving or dispersible primary seal coat and an immediate release thiazolidinedione derivative coat. The controlled release core can be any type of controlled release core such as a hydrogel matrix or osmotic tablet but **it can**

contain only one pharmaceutically active ingredient, specifically metformin.

The Vergez reference is directed to a dosage form that contains **two (2)** different active ingredients in the core, and both active ingredients are released in a controlled manner. See paragraphs 2 and 15. The fact that the present claims are limited to only one drug in the core and that only one drug is released in a controlled manner, renders the Vergez reference non analogous art to the invention recited in the pending claims.

As explained in the prior amendent, it was only after much research and experimentation that Applicants arrived at the particular arrangement of a controlled release metformin core/rapidly water soluble or water dispersible primary seal coat/immediate release thiazolidinedione derivative coat. This arrangement for a once a day product could not have been predicted or rendered obvious in view of the vastly different chemical and physical properties between metformin and the recited thiazolidinedione derivative.

Some of the important properties of the drugs that needed to be considered and evaluated during the research on the present invention were the solubility and stability of the drugs. For example, it is well known that metformin is a very soluble drug while the recited thiazolidinedione derivatives are less soluble than metformin. These vastly different solubilities needed to be accommodated in the design of a once a day oral dosage form. The Vergez reference does not provide any guidance for accommodating the different solubilities of metformin and the recited thiazolidinedione.

In addition, as evidenced by Exhibit A, it was also well known that the recited thiazolidinedione derivatives had stability issues that needed to be addressed. Exhibit A

is a collection of product information brochures for pioglitazone, troglitazone, rosiglitazone and ciglitazone that indicate the compounds should be stored at -20°C and are poorly soluble. Again, the Vergez reference fails to provide any guidance to accommodate the metformin and thiazolidinedione derivate stability issues.

It is respectfully submitted that if the teachings of the Vergez reference were followed, without the aid of hindsight, an individual of ordinary skill would not arrive at the presently claimed invention. Following the teaching of the Vergez reference, an individual of ordinary skill would develop a dosage form with the thiazolidinedione derivative in the controlled release core. Support for this assertion can be found in ¶¶ 2 and 15 and Example 7 described in paragraph 190 of the Vergez reference. ¶¶ 2 and 15 are summaries of the Vergez reference and state that the dosage forms described in the reference provide controlled release of two active ingredients. This is entirely different from the pending claims which only provide controlled release of one active ingredient. Further, Example 7 of the Vergez reference is the only example that employs a thiazolidinedione derivative and provides no guidance for preparing once a day thiazolidinedione derivative dosage forms. There are no examples that employ metformin. Example 7 places a thiazolidinedione derivative, pioglitazone, in the controlled release core and does not employ an immediate release coating. This structure is the exact opposite of the dosage form recited in the pending claims which require that thiazolidinedione derivative be released immediately from a coating applied to a rapidly dispersing or dissolving seal coat. Based upon the entire teachings of the Vergez reference, it is respectfully submitted that there is no guidance or suggestion to an

individual of ordinary skill to arrive at the invention recited in the pending claims.

It is respectfully submitted that the pending claims are patentable over the Vergez reference because the pending claims require a controlled release core with a single active ingredient, metformin, and an immediate release thiazolidinedione derivative coat applied to a rapidly dissolving or disintegrating primary seal coat. This unique dosage form is not suggested or disclosed by the Vergez reference which teaches a controlled release core with two different active ingredients in the core and a broad general disclosure of the possibility of an immediate release layer but which does not give any guidance on how to apply the immediate release layer.

Based upon the foregoing amendments and representations, Applicants respectfully requested that the rejection of the claims in the above-identified application be withdrawn. Early and favorable action is earnestly solicited.

It is believed that no fee is required for submission of this response because it is being mailed before the three month deadline, September 11, 2007. If a fee is due, the Commissioner is authorized to charge our deposit account, Account No. 08-1540.

Respectfully submitted,

Martin P. Endres
Reg. No. 35,498

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2646
(212) 302-8989

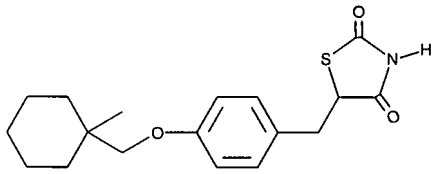
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on Sept 11, 2007

Product Information

Ciglitazone

Catalog No. 71730

CAS Registry No.:	74772-77-3
Formal Name:	5-[[4-[(1-methylcyclohexyl)methoxy] phenyl]methyl]-2,4-thiazolidinedione
Synonyms:	ADD 3878; U-63287
MF:	$C_{18}H_{23}NO_3S$
FW:	333.4
Purity:	≥98%
Stability:	≥1 year at -20°C
Supplied as:	A crystalline solid
UV/Vis.:	λ_{max}: 228, 279, 284 nm



Laboratory Procedures

Ciglitazone is an antidiabetic drug of the thiazolidinedione structural class. For long term storage, we suggest that ciglitazone be stored as supplied at -20°C. It will be stable for at least one year.

Ciglitazone is supplied as a crystalline solid. A stock solution may be made by dissolving the ciglitazone in an organic solvent purged with an inert gas. Ciglitazone is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide is a atleast 16 mg/ml.

Ciglitazone is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, ciglitazone should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Ciglitazone has a solubility of 400 µg/ml in a 1:4 solution of DMSO:PBS (pH 7.2) using this method. Store aqueous solutions of ciglitazone on ice and use within 12 hours of preparation. We do not recommend storing the aqueous solution for more than one day.

Ciglitazone is a potent and selective PPARγ ligand. It binds to the PPARγ ligand-binding domain with an EC_{50} value of 3.0 µM.[1] Ciglitazone is active *in vivo* as a anti-hyperglycemic agent in the *ob/ob* mouse model.[1]

Reference

1. Willson, T.M., Cobb, J.E., Cowan, D.J., *et al.* The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* **39**, 665-668 (1996).

Related Products

15-deoxy-$\Delta^{12,14}$-Prostaglandin J_2 - Cat. No. 18570 • GW 9962 - Cat. No. 70785 • PPARγ-PAK - Cat. No. 71000 • Rosiglitazone - Cat. No. 71740 • Rosiglitazone (potassium salt) - Cat. No. 71742 • MEDICA 16 - Cat. No. 90290 • PPARγ Polyclonal Antibody - Cat. No. 101700 • PPARγ (human) cDNA Probe - Cat. No. 601700

Cayman Chemical

Mailing address
1180 E. Ellsworth Road
Ann Arbor, MI
48108 USA

Phone
(800) 364-9897
(734) 971-3335

Fax
(734) 971-3640

E-Mail
custserv@caymanchem.com

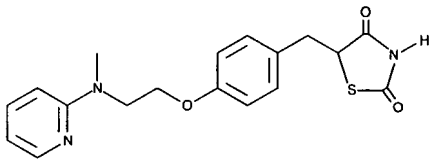
Web
www.caymanchem.com

Product Information

Rosiglitazone

Catalog No. 71740

CAS Registry No.: 122320-73-4
Formal Name: 5-[[4-(2-methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione
Synonym: BRL 49653
MF: $C_{18}H_{19}N_3O_3S$
FW: 357.4
Purity: ≥98%
Stability: ≥2 years at -20°C
Supplied as: A crystalline solid
UV/Vis.: λ_{max}: 203, 248 nm



Laboratory Procedures

For long term storage, we suggest that rosiglitazone be stored as supplied at -20°C. It will be stable for at least two years.

Rosiglitazone is supplied as a crystalline solid. A stock solution may be made by dissolving the rosiglitazone in an organic solvent purged with an inert gas. Rosiglitazone is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide. The solubility of rosiglitazone in these solvents is 1, 34, and 25 mg/ml, respectively.

Rosiglitazone is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, rosiglitazone should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Rosiglitazone has a solubility of 0.5 mg/ml in a 1:3 solution of DMSO:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Thiazolidinediones are a group of structurally related peroxisome proliferator-activated receptor γ (PPARγ) agonists with antidiabetic actions *in vivo*.[1,2] Rosiglitazone (BRL 49653) is a prototypical thiazolidinedione and has served as a reference compound for this class.[3] Rosiglitazone is a potent and selective PPARγ ligand. It binds to the PPARγ ligand-binding domain with a K_d of 43 nM.[3] It activates luciferase-based expression constructs $PPAR\gamma_1$ and $PPAR\gamma_2$ with EC_{50} values of approximately 30 nM and 100 nM, respectively.[3] Rosiglitazone is active *in vivo* as a antidiabetic agent in the *ob/ob* mouse model, and has been used as an oral hypoglycemic agent in the treatment of Type II diabetes in humans for many years.

References

1. Willson, T.M., Cobb, J.E., Cowan, D.J., *et al.* The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* **39**, 665-668 (1996).
2. Cantello, B.C.C., Cawthorne, M.A., Cottam, G.P., *et al.* [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **37**, 3977-3985 (1994).
3. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-acivated receptor γ (PPARγ). *J. Biol. Chem.* **270**, 12953-12956 (1995).

Related Products

15-deoxy-$\Delta^{12,14}$-Prostaglandin J_2 - Cat. No. 18570 • Azelaoyl PAF - Cat. No. 60924 • GW 9662 - Cat. No. 70785 • BADGE - Cat. No. 70790 • PPARγ-PAK - Cat. No. 71000 • Ciglitazone - Cat. No. 71730 • Rosiglitazone (potassium salt) - Cat. No. 71742

Cayman Chemical

Mailing address
1180 E. Ellsworth Road
Ann Arbor, MI
48108 USA

Phone
(800) 364-9897
(734) 971-3335

Fax
(734) 971-3640

E-Mail
custserv@caymanchem.com

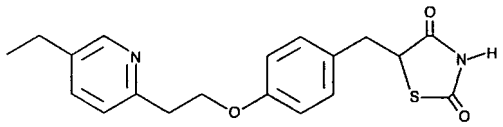
Web
www.caymanchem.com

Product Information

Pioglitazone

Catalog No. 71745

CAS Registry No.: 111025-46-8
Formal Name: 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl-2,4-thiazolidinedione
MF: $C_{19}H_{20}N_2O_3S$
FW: 356.4
Purity: ≥98%
Stability: ≥1 year at -20°C
Supplied as: A crystalline solid
UV/Vis.: λ_{max}: 267 nm



Laboratory Procedures

For long term storage, we suggest that pioglitazone be stored as supplied at -20°C. It will be stable for at least one year.

Pioglitazone is supplied as a crystalline solid. A stock solution may be made by dissolving the pioglitazone in an organic solvent purged with an inert gas. Pioglitazone is soluble in organic solvents such as DMSO and dimethyl formamide. The solubility of pioglitazone in these solvents is at least 2.5 mg/ml.

Pioglitazone is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, pioglitazone should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Pioglitazone has a solubility of 100 µg/ml in a 1:1 solution of DMSO:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Thiazolidinediones (TZDs) are a group of structurally related PPARγ agonists with anti-diabetic actions *in vivo*.[1,2] Rosiglitazone (BRL49653) is a prototypical TZD and has served as a reference compound for this class of PPARγ ligands.[3]

Pioglitazone is a closely related TZD which also selectively activates the human PPARγ-1. Pioglitazone is about one tenth as potent as rosiglitazone, with an EC_{50} of about 500-600 nM for both human and mouse PPARγ.[4,5] In a transactivation assay using COS-1 cells transfected with full length human PPARα and RXRα, pioglitazone and rosiglitazone exhibit low level activation of PPARα at 1 µM and 5.4- and 4.2-fold activation, respectively, at a concentration of 10 µM.[4]

References

1. Willson, T.M., Cobb, J.E., Cowan, D.J., *et al.* The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* **39**, 665-668 (1996).
2. Cantello, B.C.C., Cawthorne, M.A., Cottam, G.P., *et al.* [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **37**, 3977-3985 (1994).
3. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-acivated receptor γ (PPARγ). *J. Biol. Chem.* **270**, 12953-12956 (1995).
4. Sakamoto, J., Kimura, H., Moriyama, S., *et al.* Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem. Biophys. Res. Commun.* **278**, 704-711 (2000).
5. Willson, T.M., Brown, P.J., Sternbach, D.D., *et al.* The PPARs: from orphan receptors to drug discovery. *J. Med. Chem.* **43(4)**, 528-550 (2000).

Related Products

GW 9662 - Cat. No. 70785 • PPARγ-PAK - Cat. No. 71000 • Ciglitazone - Cat. No. 71730 • Troglitazone - Cat. No. 71750

Cayman Chemical

Mailing address
1180 E. Ellsworth Road
Ann Arbor, MI
48108 USA

Phone
(800) 364-9897
(734) 971-3335

Fax
(734) 971-3640

E-Mail
custserv@caymanchem.com

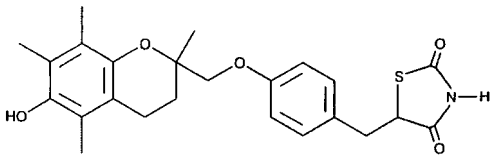
Web
www.caymanchem.com

Product Information

Troglitazone

Catalog No. 71750

CAS Registry No.: 97322-87-7
Formal Name: 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-teramethyl-2H-1-benzopryran-2-yl)methoxy]phenyl]methyl]-2,4-thiazlidinedione
Synonym: Resulin™
MF: $C_{24}H_{27}NO_5S$
FW: 441.5
Purity: ≥98%
Stability: ≥1 year at -20°C
Supplied as: A crystalline solid



Laboratory Procedures

For long term storage, we suggest that troglitazone be stored as supplied at -20°C. It will be stable for at least one year.

Troglitazone is supplied as a crystalline solid. A stock solution may be made by dissolving the troglitazone in an organic solvent purged with an inert gas. Troglitazone is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF). The solubility of troglitazone in these solvents is at least 300 µg/ml in ethanol and 30 mg/ml in DMSO and DMF.

Troglitazone is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, troglitazone should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Troglitazone has a solubility of 100 µg/ml in a 1:6 solution of DMSO:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Thiazolidinediones (TZDs) are a group of structurally related PPARγ agonists with antidiabetic actions *in vivo*.[1,2] Rosiglitazone (BRL 49653) is a prototypical TZD and has served as a reference compound for this class.[3] Troglitazone is a TZD which was approved for the treatment of insulin resistance and hyperglycemia in Type II diabetes, under the trade name Resulin™, but was withdrawn from the market due to hepatotoxicity.

Troglitazone is a potent and selective PPARγ agonist. The EC_{50} values for transactivation of human and mouse PPARγ in a cell-based assay are 0.55 and 0.78 µM, respectively.[4] In the same assay system, no activation of PPARα and PPARδ was observed at concentrations up to 10 µM. Troglitazone binds to the PPARγ ligand-binding domain (LBD) but fails to induce interaction of the PPARγ LBD with the transcriptional coactivators SRC-1, TIF2, AIB1, p300, or TRAP220.[5] Troglitazone also induces cell cycle arrest and apoptosis in several cancer cell lines with an EC_{50} of 10 µM.[6]

References

1. Willson, T.M., Cobb, J.E., Cowan, D.J., *et al.* The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* **39**, 665-668 (1996).
2. Cantello, B.C.C., Cawthorne, M.A., Cottam, G.P., *et al.* [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **37**, 3977-3985 (1994).
3. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-acivated receptor γ (PPARγ). *J. Biol. Chem.* **270**, 12953-12956 (1995).
4. Willson, T.M., Brown, P.J., Sternbach, D.D., *et al.* The PPARs: from orphan receptors to drug discovery. *J. Med. Chem.* **43(4)**, 528-550 (2000).
5. Kodera, Y., Takeyama, K., Murayama, A., *et al.* Ligand type-specific interactions of peroxisome proliferator-activated receptor γ with transcriptional coactivators. *J. Biol. Chem.* **275**, 33201-33204 (2000).
6. Yoshizawa, K., Cioca, D.P., Kawa, S., *et al.* Peroxisome proliferator-activated receptor g ligand troglitazone induces cell cycle arrest and apoptosis of hepatocellular carcinoma cell lines. *Cancer* **95(10)**, 2243-2251 (2002).

Related Products

15-deoxy-$\Delta^{12,14}$-Prostaglandin J_2 - Cat. No. 18570 • GW-9662 - Cat. No. 70785 • PPARγ-PAK - Cat. No. 71000 • Ciglitazone - Cat. No. 71730

Cayman Chemical

Mailing address
1180 E. Ellsworth Road
Ann Arbor, MI
48108 USA

Phone
(800) 364-9897
(734) 971-3335

Fax
(734) 971-3640

E-Mail
custserv@caymanchem.com

Web
www.caymanchem.com